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Important Safety Information

EPRONTIA™ (topiramate) oral solution, 25 mg/mL

Indications:

- Initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older.
- Adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older.
- Preventive treatment of migraine in patients 12 years of age and older.

Inform patients that a calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

Additional Important Safety Information

Warnings and Precautions:

Acute Myopia and Secondary Angle Closure Glaucoma: A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving EPRONTIA (topiramate). Symptoms typically occur within 1 month of initiation of EPRONTIA therapy. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Primary treatment to reverse symptoms is discontinuation of EPRONTIA.

Visual Field Defects: Visual field defects have been reported in clinical trials and post-marketing experience in patients receiving topiramate. In clinical trials, most of these events were found to be reversible after topiramate discontinuation. If visual problems occur, consideration should be given to discontinuing the drug.

Oligohydrosis (decreased sweating) and Hyperthermia: Oligohydrosis, infrequently resulting in hospitalization, has been reported in association with EPRONTIA use. The majority of these reports have been in pediatric patients. Patients, especially pediatric patients, should be monitored for evidence of decreased sweating and increase in body temperature, especially in hot weather. Caution should be used when EPRONTIA is prescribed with other drugs that predispose patients to heat-related disorders. These drugs include, but are not limited to, other carbonic anhydrase inhibitors and other drugs with anticholinergic activity.

Metabolic Acidosis: Metabolic acidosis was commonly observed in adults and pediatric patients in clinical trials and is caused by renal bicarbonate loss due to carbonic anhydrase inhibition by topiramate. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of topiramate. EPRONTIA treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus. Baseline and periodic serum bicarbonate measurements are recommended during EPRONTIA treatment. If metabolic acidosis develops, consideration should be given to either dose reduction or discontinuation of therapy using dose tapering.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including EPRONTIA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Cognitive/Neuropsychiatric Adverse Reactions: EPRONTIA can cause cognitive/neuropsychiatric adverse reactions. The most frequent adverse reactions can be classified into 3 categories: 1) cognitive-related dysfunction (confusion, difficulty with concentration, difficulty with memory, speech or language problems); 2) psychiatric/behavior disorders; 3) somnolence or fatigue.

Fetal Toxicity: EPRONTIA can cause fetal harm when administered to pregnant women. The benefits and risks should be considered when administering this drug in women of childbearing potential.

Withdrawal of Antiepileptic Drugs: EPRONTIA should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. If rapid withdrawal is required, appropriate monitoring is recommended.

Serious Skin Reactions: Serious skin reactions (Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]) have been reported. EPRONTIA should be discontinued at the first sign of a rash unless the rash is clearly unrelated to the drug. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. Inform patients about the signs of serious skin reactions.

Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid Use): Topiramate treatment can cause hyperammonemia with or without encephalopathy, the risk of which appears to be dose related, and which has been reported more frequently with concomitant use of valproic acid. In patients who develop unexplained lethargy, vomiting or changes in mental status associated with topiramate, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

Kidney Stones: EPRONTIA can cause an increased risk of kidney stones. The concomitant use of topiramate with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet, may increase the risk of kidney stone formation. Instruct patients to stay well hydrated while taking EPRONTIA.

Hypothermia with Concomitant Valproic Acid Use: Hypothermia has been reported in association with topiramate use with concomitant valproic acid both in conjunction with hyperammonemia and in the absence of hyperammonemia. Consider discontinuation of topiramate or valproate in patients who develop hypothermia. Blood ammonia levels should be assessed during clinical management.

Adverse Reactions:

The most common side effects for EPRONTIA include:

- Tingling of the arms and legs
- Not feeling hungry
- Nausea
- A change in the way foods taste
- Diarrhea
- Weight loss
- Nervousness
- Upper respiratory tract infections
- Speech problems
- Tiredness
- Dizziness
- Sleepiness/drowsiness
- Slow reactions
- Difficulty with memory
- Pain in the abdomen
- Fever
- Abnormal vision
- Decreased feeling or sensitivity, especially in the skin

These are not all the possible side effects of EPRONTIA.

Use in Specific Populations:

Women of Reproductive Potential

Women of childbearing potential who are not planning a pregnancy should use effective contraception because of the risks of oral clefts and small for gestational age (SGA).

Renal Impairment

The clearance of EPRONTIA is reduced in patients with moderate (creatinine clearance 30 to 69 mL/min/1.73 m²) and severe (creatinine clearance <30 mL/min/1.73 m²) renal impairment. A dosage adjustment is recommended in patients with moderate or severe renal impairment.

Patients Undergoing Hemodialysis

EPRONTIA is cleared by hemodialysis at a rate that is 4 to 6 times greater than in a normal individual. A dosage adjustment may be required.

The Important Safety Information does not include all the information needed to use EPRONTIA safely and effectively. Visit EPRONTIA.com for full prescribing information.

To report SUSPECTED ADVERSE REACTIONS, contact Azurity Pharmaceuticals, Inc. at 1-855-379-0383, or FDA at 1-800-FDA-1088 or www.fda.gov/MedWatch.

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azurity

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Epilepsia®

SPECIAL REPORT

ILAE clinical practice recommendations for the medical treatment of depression in adults with epilepsy

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Abstract

The aim of this document is to provide evidence-based recommendations for the medical treatment of depression in adults with epilepsy. The working group consisted of members of an ad hoc Task Force of the International League Against Epilepsy (ILAE) Commission on Psychiatry, ILAE Executive and the International Bureau for Epilepsy (IBE) representatives. The development of these recommendations is based on a systematic review of studies on the treatment of depression in adults with epilepsy, and a formal adaptation process of existing guidelines and recommendations of treatment of depression outside epilepsy using the ADAPTE process. The systematic review identified 11 studies on drug treatments (788 participants, class of evidence III and IV); 13 studies on psychological treatments (998 participants, class of evidence II, III and IV); and 2 studies comparing sertraline with cognitive behavioral therapy (CBT; 155 participants, class of evidence I and IV). The ADAPTE process identified the World Federation of Societies of Biological Psychiatry guidelines for the biological treatment of unipolar depression as the starting point for the adaptation process. This document focuses on first-line drug treatment, inadequate response to first-line

antidepressant treatment, and duration of such treatment and augmentation strategies within the broader context of electroconvulsive therapy, psychological, and other treatments. For mild depressive episodes, psychological interventions are first-line treatments, and where medication is used, selective serotonin reuptake inhibitors (SSRIs) are first-choice medications (Level B). SSRIs remain the first-choice medications (Level B) for moderate to severe depressive episodes; however, in patients who are partially or non-responding to first-line treatment, switching to venlafaxine appears legitimate (Level C). Antidepressant treatment should be maintained for at least 6 months following remission from a first depressive episode but it should be prolonged to 9 months in patients with a history of previous episodes and should continue even longer in severe depression or in cases of residual symptomatology until such symptoms have subsided.

KEYWORDS
depression, epilepsy, treatment

1 | INTRODUCTION

A lifetime history of psychiatric disorders is identified in one of every three people with epilepsy, and among all psychiatric conditions, depression is one of the most frequent.[1] A meta-analysis of 14 population-based studies, including over 1 000 000 participants, showed an overall prevalence of active (current or last 12 months) depression in epilepsy of 23.1% (95% confidence interval [CI] 20.6%–28.3%) with an increased overall risk of 2.7 (95% CI 2.09–3.6) compared with the general population.[2] These estimates, however, vary considerably across studies depending on the ascertainment source (ie, self-report vs. screening tools vs. structured clinical interviews), countries, regions, and settings.

Despite evidence that depression represents a frequently encountered comorbidity, data on the treatment of depression in epilepsy is still limited[3] and recommendations rely mostly on individual clinical experience and expertise.[4,5] Moreover, access to specialized mental health services remains highly variable around the world, especially for patients with epilepsy, with general health professionals caring for people with epilepsy needing to become familiar with the treatment of depression.[6] A systematic approach is still lacking, providing the impetus for this report to provide a first set of recommendations for the medical treatment of depression in epilepsy based on a systematic approach.

As recommended in the Clinical Practice Guideline (CPG) development protocol published by the Epilepsy Guidelines Working Group of the International League Against Epilepsy (ILAE),[7] if CPGs already exist for a specific disease, the possibility of adapting the CPGs for the new population or setting of interest should be explored. The ILAE appointed a Task Force under the Commission on Psychiatry with the aim of exploring such a possibility and developing clinical practice statements for the treatment of psychiatric disorders in epilepsy. The Task Force agreed to focus on the medical treatment of depression in adults with epilepsy, given its high prevalence and current limitations of accessing specialized mental health care. The Task Force started working on this project in 2018 with the development of the protocol and creation of a working group. The first meeting was in New Orleans in December 2018 and the last meeting in Baltimore in December 2019.

Keypoints

- Psychological treatments are first line for mild depressive episodes; where medication is used, selective serotonin reuptake inhibitors (SSRIs) are first choice
- SSRIs remain the first choice medications for moderate to severe depressive episodes
- In patients non-responding to first-line treatment, switching to venlafaxine appears legitimate
- Antidepressant treatment should be maintained for at least 6 months following remission from a first episode
- Treatment should be prolonged in cases of residual symptoms until subsided

2 | GOALS AND TARGET AUDIENCE

The main goal of this document is to provide a general framework for the medical treatment of depression in adults with epilepsy based on a systematic approach, including (a) a systematic review of studies on the treatment of depression in adults with epilepsy, and (b) a formal adaptation process of existing guidelines of treatment of depression outside epilepsy using the ADAPTE process.[8]

The present document covers the pharmacological treatment of unipolar depression in epilepsy and not depression in the context of bipolar disorder or other psychiatric disorders. It also covers stimulation techniques. It focuses on the management of the acute phase of a depressive episode and not the maintenance treatment, meaning the prophylactic treatment of depression relapse or recurrence. Treatment-resistant depression, meaning failure to respond to two courses of different antidepressants, is not covered by the present document. This report incorporates the opinions of experts in the field of epilepsy and psychiatric disorders.

The target audience of the present document includes epileptologists, neurologists, psychiatrists, neuropsychiatrists, general practitioners, nurse practitioners, clinical psychologists, and neuropsychologists, as well as any health professional dealing with adults with epilepsy.

3 | DEFINITIONS AND GENERAL PRINCIPLES

Unipolar depression comprises a heterogeneous group of different types of depression ranging from biologically determined (formerly "endogenous" or "melancholic") conditions to more event-dependent (formerly "reactive") conditions. However, in general, it has not been found useful to distinguish between these different types of depression when making pharmacological treatment recommendations.[9]

In the context of epilepsy, it is also established that the phenomenology of depression in epilepsy is sometimes characterized by atypical features that are non-adequately captured by classificatory systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). This can be due to a number of reasons, including peri-ictal symptoms and the effect of antiseizure medications (ASMs).[1] Furthermore, some patients seem to develop a pleomorphic pattern of symptoms also known as interictal dysphoric disorder, whose autonomy from other types of depression is still controversial.[10] The present document does not apply to peri-ictal depressive symptoms, ASM-induced depression, or the so-called interictal dysphoric disorder.

Remission and recovery are the main goals of the acute treatment of depression, while recurrence prevention is the primary objective of maintenance treatment. *Remission* is defined by the disappearance of all symptoms of depression while ≥50% reduction is defined as *response*. *Recovery* refers to a period of remission lasting at least 6–12 months, whereas *relapse* is used in the case of worsening or a new depressive episode before remission has turned into a recovery state. *Recurrence* is defined by the occurrence of a depressive episode after a complete recovery was achieved.[11]

In the present document, severity of depressive symptoms is defined as mild for a Beck Depression Inventory (BDI-II) score of 14–19 and moderate as 20–29, whereas severe depression is defined by a BDI score 30 or higher.[12] The panel agreed on the use of the BDI because, among the measures validated in epilepsy, it is an easily accessible self-rating scale well-known to health practitioners (eg, neurologists) around the world. In contrast, the Hamilton Depression Rating Scale needs to be administered, while the Neurological Disorders Depression Inventory for Epilepsy (NDDIE) does not provide a severity score.

In general terms, the management of depression should follow a stepped care model with multiple professionals involved, as detailed in Figure 1. The treatment of depression is based on an integrated multidisciplinary approach combining pharmacological and psychological interventions. Prior to beginning treatment, a comprehensive treatment plan should be developed based on the history of previous treatments, current clinical findings (eg, the presence of psychotic symptoms, agitation, anxiety, or atypical symptoms), severity of illness, and risk of suicide). Whenever possible, the patient's preferences and previous treatment experiences should be considered. The final judgment regarding a specific treatment must be made by the responsible treating practitioner considering the clinical picture presented by the patient and the diagnostic and therapeutic options available.

4 | METHODS AND DATA EXTRACTION

4.1 | Systematic review of studies on the treatment of depression in epilepsy

The process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

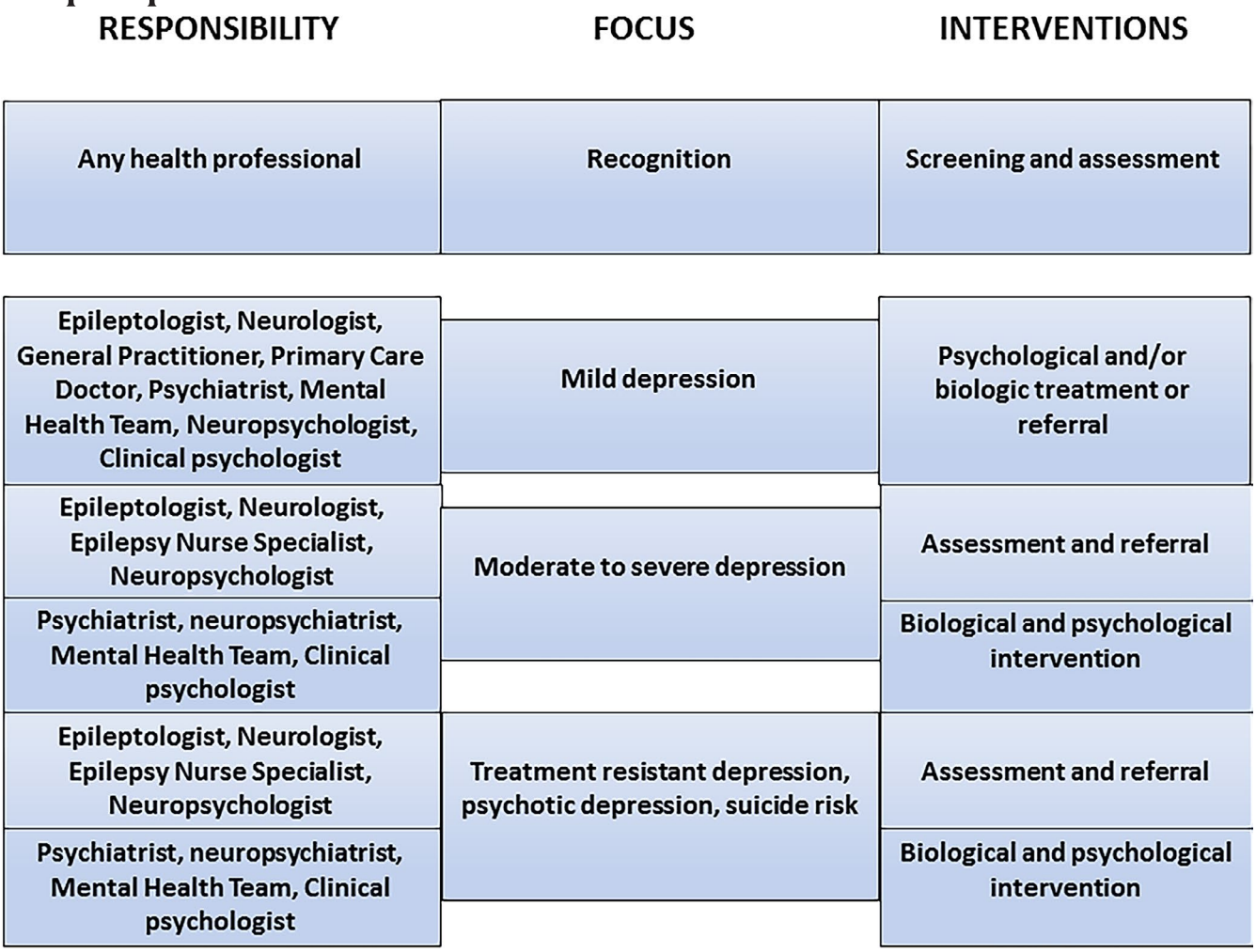

FIGURE 1 Stepped care model of depression in epilepsy

requirements and a PROSPERO protocol was developed and registered, with registration number CRD42020162332 (available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020162332). The systematic review was completed using a National Library of Medicine (MEDLINE) and Embase search with search terms "epilepsy"[MeSH Terms] OR "epilepsy"[All Fields]) AND ("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) continuously updated up to the June 1, 2020. No filters were used. Type of study to be included: randomized-controlled trials (RCTs) and open-label trials to assess the beneficial effect of treatments supplemented with observational and case - control studies. Inclusion criteria: adults with epilepsy and unipolar depression (as diagnosed using any recognized diagnostic criteria). Exclusion criteria: children and adolescents (younger than 18 years of age) and assessment of depressive symptoms in people with epilepsy without a diagnosis of depression. Conference abstracts were excluded. Outcome measure: response and remission rates from depression. Two researchers (BdT, HH) reviewed abstracts for inclusion and exclusion criteria and relevance to the research question. Then the full text of these articles was screened independently by two reviewers (MM, ALT) for inclusion and exclusion criteria. Finally, the results of each included study were classified according to the American Academy of Neurology Practice Parameter Classification (AANPPC; Appendix S1) by the working group, which allows the allocation to four classes of evidence provided by each individual study.[13] A formal qualitative data synthesis was performed summarizing data extracted.

4.2 | Systematic appraisal of treatment guidelines for depression

The ADAPTE process provides a systematic and feasible approach to modifying and adapting existing guidelines for use in different settings.[8] The process has been designed to ensure that the adapted guidelines and/or recommendations not only address specific health questions relevant to the context of use but are also suited to the needs, priorities, policies, and resources of the targeted setting. The ADAPTE process has been developed to meet the needs of different users and groups, including guideline developers, health care providers, and groups with lesser or greater resources. There are three phases: set up, adaptation, and finalization (feedback). The set-up phase involves the creation of the working group and the expert panel. The working group consisted of members of the Task Force on Identification, Treatment, and Prevention of the ILAE Commission on Psychiatry (MM, BdT, HH, KK, AMK, ALT, SJW), a representative of the ILAE Executive Committee (AG), and a representative of the International Bureau for Epilepsy (MJB). During the adaptation phase, guidelines were identified through a search in guideline clearinghouses such as the US National Guideline Clearinghouse (www.guideline.gov) and the Guidelines International Network (www.g-i-n-net), as well as through a MEDLINE search using the terms "depression", "recommendation", "standard", "guideline" limiting to publication type "guideline", "human", "adult". Guidelines older than 10 years were excluded as well as those not available in English. Titles and abstracts were screened by two reviewers (MM, ALT). Guidelines included in the final qualitative synthesis were then ranked using AGREE II by panel members. The panel then went through each recommendation of the top ranked guideline(s) taking into account evidence provided by the systematic review in order to verify the level of evidence in epilepsy. Each recommendation was accepted, modified, or rejected using a modified Delphi consensus approach (see Table S4). Consensus was set at 80%. Recommendation matrices were then developed collecting comments from panel members. Recommendations were then developed and modified according to the comments and feedback provided by the panel members. They represent the backbones of the clinical practice statements and are summarized in the accompanying paragraph. In the finalization process, a draft of this document was reviewed by members of the ILAE Commission on Psychiatry, ILAE Executive, Guidelines and Publication Committees, as well as posted on the ILAE website to be externally reviewed by target users and to receive feedback, which was then incorporated into this final report.

5 | RESULTS

5.1 | Systematic review of studies on the treatment of depression in epilepsy

A PRISMA flow diagram is shown in Figure 2 and the PRISMA Checklist is provided in Table S1. A qualitative summary of the results of the final set of studies included in the systematic review is shown in Table 1 along with the level of evidence provided by each study. A high-level summary is provided in Table 2.

Regarding pharmacological treatment, there were 11 studies assessing a total of 788 participants across 10 drugs. There were four open studies of antidepressants in small, unselected samples of people with different types of epilepsy. They included sertraline,[16,17] citalopram,[18–20] and fluoxetine[17] or other antidepressants like reboxetine[20] and mirtazapine.[20] Almost half of these studies were uncontrolled, providing either Class III (55%) or Class IV (45%) evidence. There were six controlled studies, four involving antidepressants and two about antiepileptic drugs. One was published more than 30 years ago and compares nomifensine, amitriptyline, and placebo in 45 individuals with epilepsy and depression over a period of 12 weeks.[21] Response rates of ≈43% for amitriptyline and ≈79% for nomifensine were reported, but remission rates were not provided. The other study assessed the antidepressant effect of a traditional Chinese medicine remedy, *Xylaria nigripes*, as compared to placebo in a 12-week, randomized, double-blind, controlled study in 104 people.[14] Treatment with *X. nigripes* was reported to be associated with a significant reduction in mean Hamilton Depression Rating Scale (HAM-D) scores but neither response rates nor remission rates were provided. Two studies were published in Chinese journals. One compared paroxetine with doxepin in 67 individuals with epilepsy and depression[22] while the other is a controlled trial of venlafaxine vs. no treatment in 64 individuals.[15] A response rate of 82% for paroxetine and 71% for doxepin at 8 weeks was reported,[22] whereas the other study reported a response rate of 69% for venlafaxine at 8 weeks.[15] Neither study presented data on remission rates.

Apart from these RCTs, in general terms, the drug treatment studies seem to suggest that antidepressants are well tolerated by people with epilepsy with no significant seizure aggravation. However, response rates are extremely heterogeneous, ranging from 36%[19] to 86%.[17] This high variability is likely due to the heterogeneity of participants (from newly diagnosed epilepsy to drug-resistant epilepsy) and a possible role of pharmacokinetic interactions, especially the effect of enzyme-inducing ASMs on the pharmacokinetics of antidepressants.[23] Nonetheless, all studies were concordant in reporting improvements in depression, accompanied by no reports of seizure worsening (Tables 1 and 2).

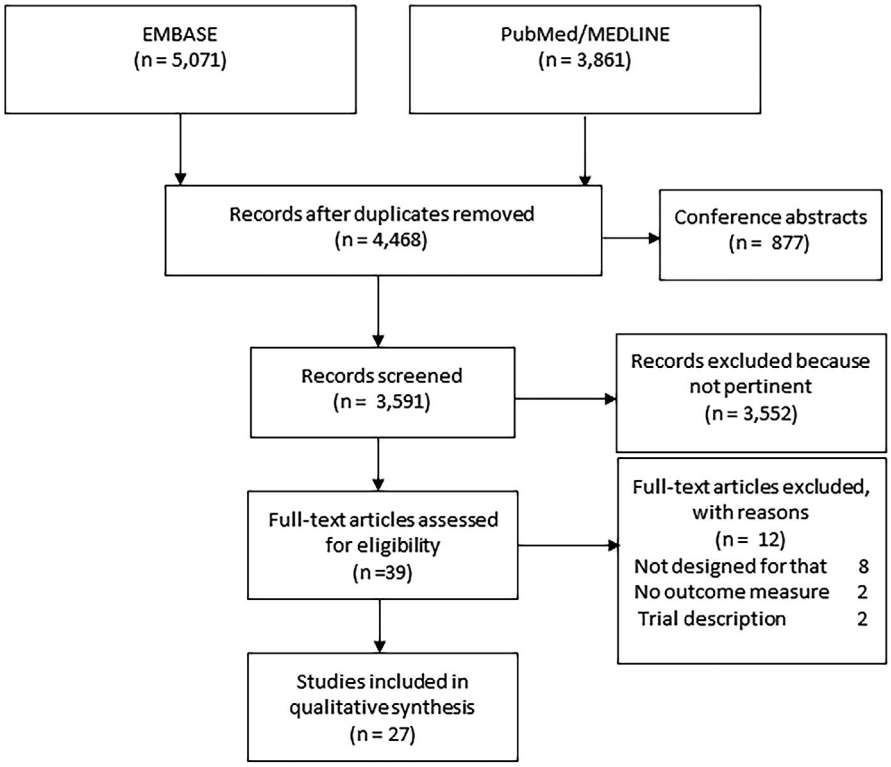

FIGURE 2 PRISMA flow diagram treatment of depression in adults with epilepsy

Two studies compared drug treatment to cognitive behavior therapy (or CBT), with one of these constituting a large RCT of 140 participants, constituting Class I evidence.[24] This study reported a remission rate of 60% for CBT and 53% for sertraline, suggesting similar treatment efficacy for CBT and antidepressants in patients with a major depressive episode (established with the MINI International Neuropsychiatric Interview) and epilepsy. Four further studies evaluated the efficacy of CBT, including three RCTs of which one targeted adults ages >60 years[25] and another employed a mindfulness based cognitive therapy (MBCT) intervention.[26] One of these studies reported a remission rate of 62% for CBT,[27] whereas two reported no effects, although the study with adults >60 years of age reported a decrease in seizure frequency.[25] The MBCT intervention showed a significant effect for depressive episodes compared with treatment as usual.[26]

Of the remaining studies focusing on psychological treatments, the systematic review identified eight studies assessing a total of 650 participants across a range of interventions, including self-management ($n = 3$), behavioral activation ($n = 2$), family therapy ($n = 1$), and psychoeducation ($n = 2$). Seven of these studies were RCTs and one employed a randomized treatment design, providing either Class II or Class III evidence. Five studies (62.5%) reported a treatment effect, mainly seen for self-management, behavioral activation, and psychoeducation interventions, whereas the remaining three reported no effect on depressive symptoms. Of the five studies examining seizure effects, none reported seizure worsening (Tables 1 and 2).

5.2 | Systematic appraisal of existing treatment guidelines for depression

The flow diagram for the guideline search is shown in Figure S1. The list of guidelines included in the qualitative synthesis is shown in Table S2. AGREE II scores of guidelines included in the qualitative synthesis are shown in Figure 3. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of unipolar depressive disorders (acute and continuation treatment)[28] and the Scottish Intercollegiate Guidelines Network (SIGN) guideline 114 for the nonpharmacological treatment of depression were ranked at the top and were identified as the starting point for the adaptation process. However, SIGN114 was withdrawn by SIGN in February 2020 as superseded and for this reason has been excluded from the subsequent adaptation phase. For this reason, this document only provides guidelines for the biological treatment of depression.

The 2013 WFSBP Guidelines are an updated version of the previous guidelines published in 2002 and 2007. The major advantage of these guidelines is that, apart from a systematic search in the MEDLINE database, the data used for the development of the guidelines come from a number of sources including pre-existing guidelines such as the Agency for Health Care Policy and Research Depression Guidelines Panel, American Psychiatric Association Practice Guideline, British Association for Psychopharmacology, Canadian Psychiatric Association, German Association

TABLE 1 Systematic review of studies on the treatment of depression in adults with epilepsy

	Reference	Design	Intervention	Duration	*N* pts	Outcome measure	Outcome for depression	Seizure worsening	Class of evidence
Drugs	Robertson & Trimble 1985[21]	RCT (fixed dose)	Nomifensine, 25 mg; amitriptyline, 25 mg; placebo	12 weeks	42	HAMD	Response rates: nomifensine, 84%; amitriptyline, 46%;	No	III
	Hovorka 2000[18]	Open prospective (flexible dose)	Citalopram	8 weeks	43	HAMD	Response rate: 65%	No	IV
	Kuhn et al. 2003[20]	Open retrospective (flexible dose)	Mirtazapine; citalopram; reboxetine	20–30 weeks	75	HAMD	Response rates: mirtazapine, 51.9%; reboxetine, 53.3%; citalopram, 36.4% (nonsignificant between groups) Remission rates: mirtazapine, 14.8%; citalopram, 21.2%; reboxetine, 20% (nonsignificant between groups)	No	IV
	Peng et al. 2015[14]	RCT (fixed dose)	*Xylaria nigripes* vs. placebo	12 weeks	104	HAMD	Response rates: *Xylaria nigripes*, 51.3%; placebo, 35.7%	No	III
	Specchio et al. 2004[19]	Open prospective (flexible dose)	Citalopram	16 weeks	45	MADRS ZDRS	Response rate: 86%	No	IV
	Ettinger 2007[57]	RCT (fixed dose)	Lamotrigine vs. placebo	12 weeks	70	BDI-II POMS CDRS	BDI-II score improvement: lamotrigine, 8.9; placebo, 1.7 POMS improvement: lamotrigine, 32.0; placebo, 6.5 CDRS improvement: nonsignificant	No	III
	Mazza 2007[58]	RCT (flexible dose)	Oxcarbazepine (OXC) vs. other AEDs	3 months	80	HAMD CDRS BDI	CDRS scores Oxcarbazepine: from 26.9 to 17.9 Controls: from 24.2 to 22.1 ($p = .02$) BDI and HAMD nonsignificant	No	III

(Continues)

TABLE 1 (Continued)

	Reference	Design	Intervention	Duration	*N* pts	Outcome measure	Outcome for depression	Seizure worsening	Class of evidence
	Fakhoury 2008[59]	Open prospective	Four phases: - Lamotrigine escalation - Lamotrigine maintenance or adjunctive phase; - Concomitant antiepileptic drugs - Lamotrigine monotherapy	36 weeks	40	BDI CES-D NDDI-E POMS	Adjunctive phase (baseline vs. end): CES-D score improvement: 10.7 POMS score improvement: 27.1 Monotherapy phase (baseline vs. end): BDI score improvement: 10.5 CES-D score improvement: 13.4 NDDI-E score improvement: 3.9 POMS score improvement: 41.6	Not reported	IV
	Fakhoury 2007[60]	Open Prospective (flexible dose)	- Adjunctive treatment with lamotrigine - Conversion to monotherapy with lamotrigine	55 weeks (19 weeks of adjunctive treatment and 36 weeks following conversion to monotherapy)	158	MINI CES-D BDI CDRS POMS	Total mood score (considering all scales) in the end of adjunctive phase decrease 27 ± 35.5 and in the end of monotherapy phase decrease 35 ± 37.5	No	IV
	Li 2005[22]	RCT (flexible dose)	Paroxetine (20 mg–40 mg/day) vs doxepin (mean dose 100 mg/day)	8 weeks	67	HAMD	Responder rates: paroxetine, 82%; doxepin, 71%	Not reported	III
	Zhu 2004[15]	RCT (flexible dose)	Venlafaxine (25 mg–75 mg/day) vs. no treatment	8 weeks	64	HAMD	Responder rates: venlafaxine, 69% No treatment, 19%	Not reported	III
Drug vs. CBT,	Orjuela –Rojas 2015[61]	Open (flexible dose)	SSRI vs. CBT	12 weeks	15	MINI BDI	Remission rate: SSRIs 87% CBT 57%	No	IV
	Gilliam 2019 [24]	RCT (flexible dose)	Sertraline vs. CBT	16 weeks	140	MINI BDI	Remission rates: sertraline, 53%; CBT 60% BDI score Sertraline: from 24.2 to 12.3 CBT: from 26.9 to 12.8	No	I

TABLE 1 (Continued)

	Reference	Design	Intervention	Duration	*N* pts	Outcome measure	Outcome for depression	Seizure worsening	Class of evidence
Psychological interventions	Sajatovic et al. 2016[62]	RCT	TIME (target self-management) vs. TAU	16 weeks	44	MINI MADRS	RR not specified MADRS reduction in the intervention group with effect size 0.70	No	III
	Ciechanowski 2010[63]	RCT	PEARLS (problem solving, behavioral activation, and psychiatric consultation) vs. TAU	12 months	40 per group	PHQ9 ≥10 HSCL−20	HSCL−20 treatment effect: PEARLS −0.56 TAU −0.11	No	III
	Chaytor 2011[64]	RCT	PEARLS (problem solving, behavioral activation, and psychiatric consultation) vs. TAU	18 months	58	SCID PHQ9 HSCL−20	HSCL−20 reduction: PEARLS 17.8% TAU 1%	No	III
	Crail Melendez 2012[27]	Open	CBT	16 weeks	23	MINI	Remission rate: 62%	No	IV
	McLaughlin 2011[25]	RCT	CBT	6 weeks	37 (>60 years)	CIDI	No main effect	Reduction in seizure frequency	III
	Thompson 2015[26]	RCT cross-over	Mindfulness-based cognitive therapy (MBCT) vs. TAU	MBCT =10 weeks TAU =20 weeks	128	PHQ9 BDI NDDI-E	Depressive episode: MBCT 0% TAU 10.7%	No	III
	Etemadifar 2018[65]	Randomized study	Family-centered empowerment programs vs. TAU	4 weeks (intervention) 2 months (postintervention)	100	DASS	No difference	Not reported	III
	Fraser 2015[66]	RCT	PACES (self-Management interventions) vs. TAU	8 weeks (intervention) 6 months (postintervention)	83	PHQ9 GAD7	PHQ9 treatment effect −1.72 ($p = .002$)	Not reported	II
	Gandy 2014[67]	RCT	CBT vs. WLC	9 weeks (intervention) 3 months (follow-up)	59	NDDI-E ≥15 HADS-D	NDDI-E and HADS-D scores non-significant difference	Not reported	III
	Novakova 2019[68]	RCT	Immediate self-help intervention (IG) vs. delayed (DG)	1 month	71	NDDI-E	NDDI-E score Non-significant difference	No	III

(Continues)

TABLE 1 (Continued)

	Reference	Design	Intervention	Duration	*N* pts	Outcome measure	Outcome for depression	Seizure worsening	Class of evidence
	Meyer 2019[71]	RCT	eCBT vs. TAU	9 months	100 per group	NDDI-E PHQ9	Significant NDDI-E and PHQ9 score reduction	Not reported	III
	Olley 2001[69]	RCT	Psychoeducation vs. WLC	2 days (intervention) 2 months (follow-up)	30	BDI	BDI score: Intervention group: 15.00–1.47 WLC: 15.10–10.0 ($p < .01$)	Not reported	III
	Zheng 2019[70]	RCT	Psychoeducation vs. TAU	12 months	184	BDI	Patients with depression Intervention group: 21.7%–10.9% TAU group: 17.4%–13.0%	No	III
Others	Baxendale 2013[49]	RCT	Bright light therapy vs. placebo (low intensity)	12 weeks	101	HADS-D	HADS-D score Non-significant difference (drop out 42.6%)	No	IV

Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; CDRS, Cornell Dysthymia Rating Scale; CES-D, Center for Epidemiological Studies Depression Scale; CIDI, Composite International Diagnostic Interview; DASS, Depression Anxiety Stress Scale; GAD-7, Generalized Anxiety Disorder 7; HADS-D, Hospital Anxiety Depression Scale-Depression Subscale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; MINI, Mini International Neuropsychiatry Inventory; NDDIE, Neurological Disorders Depression Inventory for Epilepsy; PHQ9, Patient Health Questionnaire 9; POMS, Profile of Mood States Scale; RCT, randomized controlled trial; SCID, Structured Clinical Interview for DSM; TAU, treatment as usual; WLC, waiting list control.

of Psychiatry, the National Institute for Clinical Excellence, SIGN, American College of Physicians, and the Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. Recommendations were developed and modified according to the comments and feedback provided by the panel members. Consensus was reached at the first round with only one recommendation rejected (sleep deprivation described in Section 7.9).

6 | CLASSIFICATION OF RECOMMENDATIONS

In the WFSBP guidelines, clinical evidence was based on six categories, and recommendations were defined on five grades according to Bandelow et al.[29] (Table S3). When no informative external evidence was available to answer the clinical question, WFSBP recommendations were made as "clinical consensus" (CONS).

Evidence from studies in epilepsy were classified jointly according to the American Academy of Neurology (AAN).[13] Recommendation matrices were developed by ILAE Task Force members in a meeting in Baltimore in 2019 and in subsequent virtual discussions. When no informative external evidence was available, recommendations were classified as "U" (Unknown). If the original WFSBP recommendation was based on consensus, this was again discussed, and if agreed, the recommendation was defined as "U CONS."

7 | RECOMMENDATIONS FOR PEOPLE WITH EPILEPSY

7.1 | First-line treatment

For mild depressive episodes, psychological interventions are treatment alternatives to antidepressants. Where medication is used (wish/preference of the patient, positive experience of the patient with response to medication treatment in the past, moderate or severe episodes in the past or if initial non-pharmacological treatments failed or are unavailable), SSRIs are first-choice medications.

RECOMMENDATION LEVEL: WFSBP = 1; ILAE = B

TABLE 2 High Level Summary of studies of treatment of depression in adults with epilepsy

	Studies (*n*)	Design	Participants (*N*)	Treatment effect	Seizure effect	Evidence Class
Drug treatment	11	6 RCT 5 Open	788	RR range 36%–86%[b]	8/8 nil 3 missing	6 III 5 IV
Drug vs. CBT	2	1 RCT 1 Open	155	CBT = Drug Drug > CBT	2/2 nil	1 I 1 IV
CBT	5	4 RCT 1 Open	347	Remission rate 62% MBCT/ eCBT > TAU 2 No effect	2/4 nil 1/4 reduction 2 missing	4 III 1 IV
Other psychological interventions[a]	8	7 RCT 1 Randomized	650	6 Yes 2 No	5/5 nil 3 missing	1 II 7 III

Abbreviations: CBT, cognitive behavioral therapy; ECBT, electronically delivered CBT; MBCT, mindfulness-based cognitive therapy; RCT, randomized controlled trial; RR, response rate; TAU, treatment as usual.

[a]This category includes a mixture of interventions, such as self-management (3), behavioral activation (2), mindfulness (1), family therapy (1), and psychoeducation (2).

[b]These data were derived from the seven studies reporting response rates, including RRs for >1 drug. One study reported a placebo RR of 36% and another a "no treatment" RR of 19%. Four studies reported changes associated with drug treatment in terms of questionnaire scores.

For moderate to severe depressive episodes, selective serotonin reuptake inhibitors (SSRIs) remain first-choice medications.

In patients with depression without epilepsy, data from the large-scale, real-world, National Institute of Mental Health (NIMH)–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed response rates of 47%, with remission rates (defined by a total HDRS score <7) of 27.5% at 14 weeks of treatment.[30] Studies in people with epilepsy showed overall response rates of up to 97%[17] and remission rates up to 53%.[24] In all studies published in epilepsy (see Table 1), it is not possible to differentiate treatment outcome according to severity of depressive symptoms at baseline. All studies included patients with symptom severity from mild to severe with a mean score in the moderate range. However, all studies are concordant, with no conflicting results about efficacy of SSRIs in the treatment of depression in people with epilepsy.

It has to be acknowledged that there is considerable debate in the psychiatric literature about the treatment of mild depression in adults. A patient-level meta-analysis pointed out that the magnitude of benefit of antidepressant medications compared with placebo increases with severity of depression symptoms and it may be minimal or nonexistent, on average, in patients with mild or moderate symptoms.[31]

Data about the use of ***ASMs for the treatment of depression in adults with epilepsy are almost non-existent with only one open and one RCT on Lamotrigine and Oxcarbazepine, respectively, providing low evidence.

Psychological interventions should be considered an initial treatment modality for patients with mild depression. Furthermore, psychological treatment is recommended in combination with antidepressants for patients with moderate to severe depression and for patients with only partial responses to antidepressant medications or problems with adherence to antidepressants. Patient preference for antidepressant medications or psychological treatment and their availability should be considered when deciding between initiating treatment with antidepressants or psychological treatment.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = C

Cognitive behavioral therapy (CBT) is currently the psychological intervention with the best evidence in people with epilepsy and mild to moderate depressive symptoms (Table 1). This is further discussed in a recent ILAE report on psychological interventions in epilepsy.[32] The evidence for other treatments is more mixed, in part likely reflecting the small number of studies examining each specific intervention. This highlights the need for increased clinical research efforts in this area, with carefully designed studies examining the efficacy of self-management, behavioral

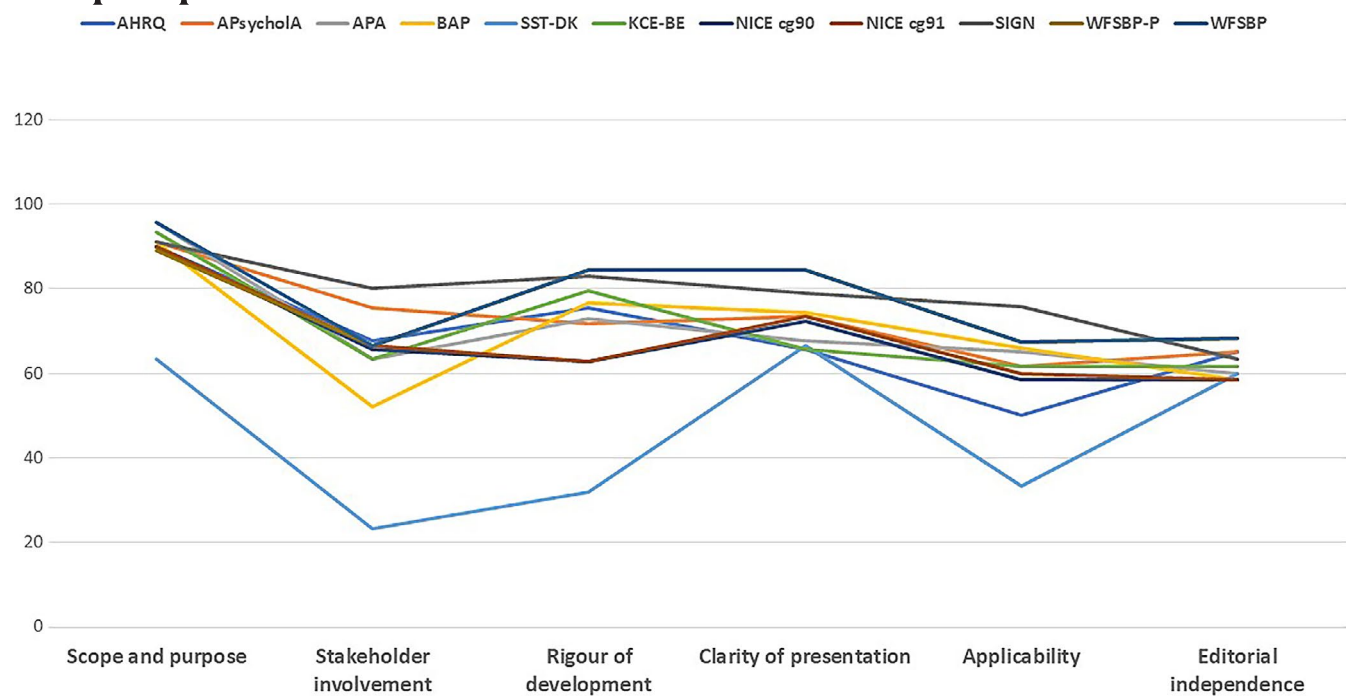

FIGURE 3 AGREE II scores for identified guidelines. AHRQ, Agency for Healthcare Research and Quality; APA+, American Psychiatry Association; APsycholA, American Psychological Association; BAP, British Association of Psychopharmacology; KCE-BE, Belgian Healthcare Knowledge Centre; NICE, National Institute of Clinical Excellence; SIGN, Scottish Intercollegiate Initiative; SST-DK, Danish Health Authority; WFSBP, World Federation of Societies of Biological Psychiatry

activation, and psychoeducation interventions promising to yield the best results.

One study compared the antidepressant efficacy of sertraline and CBT in major depressive episodes in 140 patients with epilepsy and demonstrated remission rates of 53% and 60%, respectively, which is almost double the remission rates reported for major depressive episodes in the general population.

7.2 | Special precautions

The potential risks should be carefully balanced with the benefits of antidepressant treatment. Consideration of the individual's past history including risk factors for suicidal behaviour and close observation of the patient during the first weeks of treatment are recommended when starting antidepressant treatment.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

If the patient has suicidal thoughts or intent, they should be referred to a psychiatrist for urgent review. Close surveillance and specialist treatment are necessary and admission to a psychiatric ward may be considered. Hospital admittance without patient consent may be necessary. Immediate and intensive care should be initiated and should include intensive pharmacotherapy and psychological treatment addressing biological, psychological and psychosocial factors.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

For severely depressed patients, consider the risk of overdose when antidepressant medications are prescribed.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

It is established that suicide is more frequent in people with epilepsy as compared to the general population.[33] This is even more relevant in the context of depression. Risk assessment and suicide prevention protocols for people with epilepsy are urgently needed.

Patients with psychotic depression should always be referred to a psychiatrist for urgent review and a combination of an antidepressant with an antipsychotic medication is recommended when treatment is initiated.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = U CONS

All enzyme-inducing ASMs reduce antipsychotic drug levels but the interaction is particularly evident with quetiapine. The combined treatment with carbamazepine leads to undetectable levels even at a dose of 700 mg.[23] There is no evidence that antipsychotics affect the blood levels of ASM.

Selective serotonin reuptake inhibitors (SSRIs) are not associated with seizure worsening in people with epilepsy.

RECOMMENDATION LEVEL: ILAE = C

The analysis of seizure incidence in Phase II–III studies of psychotropic drugs approved by the US Food and Drug Administration between 1985 and 2004 involving over 75 000 individuals showed that seizure incidence during treatment with SSRIs was not different from that of placebo. For tricyclics, high-dose clomipramine (>150 mg), showed a standardized incidence ratio (SIR) of 4 (95%CI 2.6–6.0).[34] Bupropion immediate-release formulation showed also a slightly increased incidence with a SIR 1.58 (95% CI 1.03–2.32).[34] However, seizure rate for the sustained-release formulation was reported similar to that of SSRIs and in the region of 0.1% at doses of up to 300 mg per day.[35] These data come from studies in people without epilepsy; however, studies in people with epilepsy identified in this systematic review are concordant, with no conflicting results about the lack of worsening in seizure control for SSRIs (Tables 1 and 2).

7.3 | Inadequate response to first-line antidepressant

In the case of inadequate response to antidepressant treatment, assessing adherence to the current treatment regimen is recommended as a first step.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

In patients partially or non-responding to first-line treatment, switching from an SSRI to venlafaxine appears appropriate.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = C

If antidepressants that are inhibitors of cytochrome P450 (CYP) isoenzymes are combined with other medications metabolized by the same CYP isoenzymes, interactions and dose adjustment according to clinical response should be considered.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

Antidepressants have complex metabolism potentially leading to some pharmacological interactions.[36] Dose adjustments do not seem to be needed for tricyclics (TCAs) in routine clinical practice for a number of pharmacokinetic reasons.[23] All enzyme-inducing ASMs seem to reduce the levels of SSRI antidepressants by around a quarter. There is no evidence, however, that these changes are clinically relevant, and dose adjustments in routine clinical practice are not needed.[23] Conversely, fluoxetine, fluvoxamine and, to a lesser extent, sertraline are inhibitors of CYP2C9 and may potentially increase the levels of phenytoin and, to a lesser extent, valproate.[23,36] Enzyme-inducing epilepsy drugs, such as carbamazepine, reduce the blood levels of bupropion by 90%, making this interaction clinically relevant.[36]

7.4 | Duration of the antidepressant treatment

Antidepressant treatment should be maintained for at least 6 months following remission from a first depressive episode. Antidepressant treatment should be prolonged to 9 months in patients with a history of long previous episodes and should continue longer in cases of residual symptomatology and until such symptoms have subsided and in those with severe depression.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

It is recommended that the same antidepressant successfully used to achieve response/remission in the acute-phase therapy be continued at the same dose during the continuation phase. If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended in the case of first episodes. Patients should be carefully monitored during the discontinuation to ensure the stability of the remission. If tapering off results in a return of symptoms, the medication should be reinstated in the original dose for at least another 6 months before attempting discontinuation again.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = U CONS

Step-down discontinuation within a period of 1–4 weeks is recommended rather than abrupt discontinuation, as this may cause discontinuation symptoms.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

There are no studies in epilepsy about the duration of the treatment and discontinuation regimen. However, there is no reason, at present, to justify longer or shorter treatment durations in people with epilepsy as compared to those without.

7.5 | Monotherapy augmentation strategies

Combination of an SSRI with an inhibitor of presynaptic autoreceptors, like mirtazapine, can be considered when monotherapy fails. The combination of venlafaxine with mirtazapine may be accompanied by worsening side effects.

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

In people with depression it is established that around two thirds of patients do not achieve full remission with first-line treatment. In people with epilepsy, current data show that up to 50% of patients do not achieve full remission from depression. For this reason, augmentation strategies are often needed. They should be adopted by psychiatrists, neuropsychiatrists, or mental health professionals familiar with such therapeutic strategies.

The combination of selective serotonin reuptake inhibitors (SSRIs) and mirtazapine is well established in patients with depression without epilepsy. Data from epilepsy populations suggest that both drugs are effective and well tolerated in monotherapy.

Adding lithium to ongoing antidepressant treatment is recommended in case monotherapy fails. Lithium augmentation should be administered for 2–4 weeks in order to allow assessment of the patient's response. The recommended lithium serum target levels are 0.6–0.8 mmol/L. In case of response, lithium augmentation should be continued for at least 12 months. In the epilepsy population, if lithium needs to be considered after monotherapy failure as augmentation, this should be used with caution given the tolerability profile and should be prescribed only by psychiatrists. Consider interactions with antiseizure medications.

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

The use of lithium in epilepsy is rarely considered. Lithium is associated with an increased risk of thyroid toxicity, especially when in combination with carbamazepine.[37] Still, lithium may prevent or mask carbamazepine or oxcarbazepine-related hyponatremia.[38] The combination lithium-valproate is associated with an increased risk of tremor, sedation, and weight gain, while the prescription with

topiramate can reduce lithium clearance potentially leading to toxic levels.[39] For the remaining antiepileptic drugs there is no evidence of major problems. In terms of proconvulsant effect, seizures seem to occur in the context of toxic lithium levels (higher than 3 mmol/L).[40] The majority of centers consider a therapeutic level between 0.4 and 0.8 mmol/L for the prophylactic treatment of mood episodes and between 0.6 and 1.0 mmol/L for the acute treatment of mania.[41] Symptoms of toxicity start for levels above 1.5 mmol/L, but it is advisable to always maintain concentrations below 1.0 mmol/L.

The augmentation of antidepressants with quetiapine or aripiprazole represents an alternative to lithium augmentation and is recommended in case monotherapy fails. Potential unwanted effects include sedation (quetiapine), weight gain (quetiapine, and to a lesser extent aripiprazole), and akathisia (aripiprazole).

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

Additive sedation with antipsychotics seems to be relevant for many ASMs while additive weight gain is particularly evident for olanzapine in combination with valproate, pregabalin, gabapentin, and carbamazepine.[42,43]

Regarding risk of seizures with antipsychotics, data from patients with a primary psychiatric disorder show that olanzapine and quetiapine are associated with a slightly increased risk while all other antipsychotics, such as risperidone, show no difference from placebo.[34] A large community-based study comparing first- and second-generation antipsychotics showed that first-generation compounds such as chlorprothixene, thioridazine, and haloperidol have a slighter higher risk than second-generation agents such as risperidone and aripiprazole.[44]

7.6 | Other pharmacological treatments

Hypericum (St. John's-Wort) may be an option in patients with mild depression who prefer "alternative medicine," but intensive education about potential side effects including seizure relapse and interactions has to be provided and potential drug interactions have to be monitored.

RECOMMENDATION LEVEL: WFSBP = 2; ILAE = U CONS

There is evidence in patients with mild-to-moderate depression without epilepsy that Hypericum (St John's-Wort) has comparable efficacy and safety when compared to SSRIs.[45] However, Hypericum is a potent inducer of CYP3A4 and P-glycoprotein (PgP) and it may inhibit or induce other CYPs, depending on the dose, route, and duration of administration.[46] In addition, data on seizure risk with Hypericum are not conclusive.[47] For all these reasons, this treatment option should be very carefully considered in epilepsy and only in very selected cases under close monitoring.

7.7 | Electroconvulsive therapy

Prior to electroconvulsive therapy (ECT) treatment implementation, a thorough medical evaluation of the patient must be performed in close collaboration with an anaesthesiologist. Caution is indicated in patients with evidence of increased intracranial pressure or cerebrovascular fragility, in patients with cardiovascular disease, for example, recent myocardial infarction, myocardial ischemia, congestive heart failure, cardiac arrhythmias or pacemakers, or abdominal aneurysm, and in patients with severe osteoporosis. ECT should only be performed by a psychiatrist who is experienced with this treatment intervention, and where possible, a baseline assessment of neuropsychological functioning should be obtained to allow careful monitoring of any adverse cognitive effects.

RECOMMENDATION LEVEL: WFSBP = CONS; ILAE = U CONS

The antiseizure properties of ECT are very well known[48] and case series and case reports have shown that ECT can even be used in the treatment of status epilepticus.[49] For this reason, the use of ECT is not contraindicated and can be used in selected cases, taking into account that data in patients with epilepsy and depression are not available. However, the cognitive adverse effects of ECT should be considered and systematically assessed by neuropsychological testing where possible, especially the effects on memory functioning. ECT is associated with retrograde amnesia, which may extend back months or years, and this seems to be more pronounced with bilateral than unilateral ECT.[50] There are no data on the consequences of ECT on memory functioning in people with epilepsy.

The indications for electroconvulsive therapy (ECT) as a first-line treatment include severe major depression with psychotic features, severe major depression with psychomotor retardation, "true" treatment-resistant major depression, refusal of food intake, or in other special situations when rapid relief from depression is required (eg, in severe suicidality) or medication is contraindicated (eg, in pregnancy). ECT as a first-line approach may also be indicated in patients who have experienced a previous positive response to ECT, and in patients who prefer ECT for a specific reason. ECT should be performed only by a psychiatrist who is experienced with this treatment intervention and neuropsychological effects (eg, on memory function) should be carefully monitored.

RECOMMENDATION LEVEL: WFSBP = 4; ILAE = U CONS

7.8 | Other treatments

Light therapy is an option in treatment of seasonal affective disorder (SAD) if administration is possible and protocol adherence can be ensured.

RECOMMENDATION LEVEL: WFSBP = 3; ILAE = U CONS

In previous classificatory systems, SAD was a distinct subtype of recurrent major depression that manifests with a seasonal pattern. In DSM-5 it is a pattern of a major depressive disorder. In order to fulfill the criteria for a seasonal pattern, depression should be present only at a specific time of year (eg, in the fall or winter) and full remission occurs at a characteristic time of year (eg, spring). An individual should demonstrate at least two episodes of depressive disturbance in the previous 2 years, and seasonal episodes should substantially outnumber nonseasonal episodes. The preferred device for light therapy is a fluorescent light box (which provides white fluorescent light with ultraviolet wavelengths filtered out) that produces light intensities greater than 2500 lux. The starting "dose" for light therapy is 10 000 lux for 30–40 min per day, administered each morning for a 2– to 4-week period. Alternatively, light boxes emitting 2500 lux require 2 h of exposure per day. In epilepsy, there is a single study that suggests a potential positive effect.[51] The protocol comprised 10 000 lux at 61 cm for 20 min, showing no difference as compared to placebo. However, the drop-out rate was almost 50%. The effect of light therapy in people with epilepsy is still largely unknown and should be considered carefully in people with photosensitive epilepsy.

Exercise training can be used as an adjunct to medication treatment for patients with mild to moderate depression.

RECOMMENDATION LEVEL: WFSBP = 3; SIGN2; ILAE = U CONS

Risks and benefits of structured exercise should be individualized depending on seizure control.

Vagus nerve stimulation (VNS) may be an option in patients with depression with insufficient response to trials of pharmacotherapy but consider that parameters used for the treatment of epilepsy may differ from those used for the treatment of depression.

RECOMMENDATION LEVEL: WFSBP = 5; ILAE = U CONS

Despite a large number of studies investigating the effect of VNS on symptoms of depression in people with epilepsy, studies investigating the efficacy of VNS on patients with epilepsy and a diagnosis of depression at baseline as the primary outcome are more scant. An audit of 59 patients with epilepsy and depression assessed before and after 1 year from VNS surgery showed a significant improvement in depressive symptoms measured with the Montgomery-Asberg Depression Rating Scale and the BDI.[52] Data on the optimal stimulation parameters to treat depression in epilepsy are not available.[53] Data from patients with treatment resistant depression showed a negative correlation between total charge delivered per day and depressive symptoms measured with the BDI, suggesting a greater antidepressant efficacy at high doses up to 2.5 mA.[54] However, no protocols are available in epilepsy and depression.

Repetitive transcranial magnetic stimulation (rTMS) may be an option in patients with depression with insufficient response to trials of pharmacotherapy but consider that parameters used for the treatment of depression may differ from those safely used to treat epilepsy.

RECOMMENDATION LEVEL: WFSBP = 5; ILAE = U CONS

rTMS is FDA approved for depression.[55] Treatments are usually delivered at 120% of the motor threshold over the left dorsolateral prefrontal cortex, which is defined as a target 5 cm anterior to the motor threshold target of the primary motor cortex. A frequency of 10 Hz is used, and pulses are clustered into 4-s trains (10 pulses/s × 4 s = 40 pulses per train), for a total of 3000 pulses per session.[53] However, data in people with epilepsy and depression about safety and efficacy are lacking.

Transcranial direct current stimulation (tDCS) has been used in the treatment of a number of neurological and psychiatric disorders with more data available for depression and pain.[56,57] A systematic review of the literature showed that anodal left dorsal prefrontal cortex tDCS is definitely effective in improving depression in major depressive disorder.[57] In epilepsy, data are still limited but suggest that cathodal tDCS is probably safe (no increase in seizures) and effective (decreased seizures).[57] A double-blinded, sham-controlled, randomized, parallel-group study of 5 days of fixed-dose (2 mA, 20 min) tDCS in 37 patients with well-controlled temporal lobe epilepsy showed an improvement in depressive symptoms as measured with the BDI, with no effect on delayed or working memory performance, no increase in seizure frequency, and no effect on interictal discharge frequency during the 4-week follow-up.[58]

7.9 | Other issues

For depression outside epilepsy, sleep deprivation, also known as "wake therapy," may be used to treat unmedicated depressed patients, or be started at the same time as an antidepressant medication with the goal of accelerating the response to medication. However, this treatment is contraindicated in people with epilepsy and depression given that sleep deprivation is a well-known trigger for seizures and can decompensate seizure control in predisposed individuals.

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CONFLICT OF INTEREST

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